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## **Use it or lose it! Cognitive activity as a protective factor for cognitive decline associated with Alzheimer's disease**

Mistridis, Panagiota ; Mata, Jutta ; Neuner-Jehle, Stefan ; Annoni, Jean-Marie ; Biedermann, Andreas ; Bopp-Kistler, Irene ; Brand, Dominique ; Brioschi Guevara, Andrea ; Decrey-Wick, Hedi ; Démonet, Jean-François ; Hemmeter, Ulrich ; Kressig, Reto W ; Martin, Brian ; Rampa, Luca ; Savaskan, Egemen ; Stuck, Andreas E ; Tschopp, Philipp ; Zekry, Dina ; Monsch, Andreas U

**Abstract:** Because of the worldwide aging of populations, Alzheimer's disease and other dementias constitute a devastating experience for patients and families as well as a major social and economic burden for both healthcare systems and society. Multiple potentially modifiable cardiovascular and lifestyle risk factors have been associated with this disease. Thus, modifying these risk factors and identifying protective factors represent important strategies to prevent and delay disease onset and to decrease the social burden. Based on the cognitive reserve hypothesis, evidence from epidemiological studies shows that low education and cognitive inactivity constitute major risk factors for dementia. This indicates that a cognitively active lifestyle may protect against cognitive decline or delay the onset of dementia. We describe a newly developed preventive programme, based on this evidence, to stimulate and increase cognitive activity in older adults at risk for cognitive decline. This programme, called "BrainCoach", includes the technique of "motivational interviewing" to foster behaviour change. If the planned feasibility study is successful, we propose to add BrainCoach as a module to the already existing "Health Coaching" programme, a Swiss preventive programme to address multiple risk factors in primary care.

DOI: <https://doi.org/10.4414/smw.2017.14407>

Posted at the Zurich Open Repository and Archive, University of Zurich

ZORA URL: <https://doi.org/10.5167/uzh-143503>

Journal Article

Published Version



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Originally published at:

Mistridis, Panagiota; Mata, Jutta; Neuner-Jehle, Stefan; Annoni, Jean-Marie; Biedermann, Andreas; Bopp-Kistler, Irene; Brand, Dominique; Brioschi Guevara, Andrea; Decrey-Wick, Hedi; Démonet, Jean-François; Hemmeter, Ulrich; Kressig, Reto W; Martin, Brian; Rampa, Luca; Savaskan, Egemen; Stuck, Andreas E; Tschopp, Philipp; Zekry, Dina; Monsch, Andreas U (2017). Use it or lose it! Cognitive activity as a protective factor for cognitive decline associated with Alzheimer's disease. *Swiss Medical Weekly*, 147:w14407.

DOI: <https://doi.org/10.4414/smw.2017.14407>

## Use it or lose it! Cognitive activity as a protective factor for cognitive decline associated with Alzheimer's disease

Panagiota Mistridis<sup>a</sup>, Jutta Mata<sup>b</sup>, Stefan Neuner-Jehle<sup>c,d</sup>, Jean-Marie Annoni<sup>e</sup>, Andreas Biedermann<sup>f</sup>, Irene Bopp-Kistler<sup>g</sup>, Dominique Brand<sup>h</sup>, Andrea Brioschi Guevara<sup>i</sup>, Hedi Decrey-Wick<sup>j</sup>, Jean-François Démonet<sup>k</sup>, Ulrich Hemmeter<sup>k</sup>, Reto W Kressig<sup>l,m</sup>, Brian Martin<sup>n,o</sup>, Luca Rampa<sup>p</sup>, Egemen Savaskan<sup>q</sup>, Andreas E. Stuck<sup>r</sup>, Philipp Tschopp<sup>s</sup>, Dina Zekry<sup>t</sup>, Andreas U. Monsch<sup>a,l</sup>

<sup>a</sup> Memory Clinic, University Centre for Medicine of Aging, Felix Platter Hospital, Basel, Switzerland

<sup>b</sup> Health Psychology, Department of Social Sciences, University of Mannheim, Germany

<sup>c</sup> Institute of Primary Care, University of Zurich and University Hospital Zurich, Switzerland

<sup>d</sup> Swiss College of Primary Care Medicine, Fribourg, Switzerland

<sup>e</sup> Neurology Unit, Department of Medicine, Faculty of Science, University of Fribourg, Switzerland

<sup>f</sup> Public Health Services, Berne, Switzerland

<sup>g</sup> Memory Clinic, University Clinic of Geriatrics, Stadtspital Waid, Zurich, Switzerland

<sup>h</sup> General Practitioner, Internal Medicine and Geriatrics, Courtelary, Switzerland

<sup>i</sup> Leenaards Memory Centre, University Hospital Lausanne, Switzerland

<sup>j</sup> General Practitioner, Corseaux, Switzerland

<sup>k</sup> Psychiatric Services St Gallen-North, Centre of Education and Research (COEUR), St Gallen, Switzerland

<sup>l</sup> University of Basel, Switzerland

<sup>m</sup> University Centre for Medicine of Aging, Felix Platter Hospital, Basel, Switzerland

<sup>n</sup> Chief Medical Officer of the Canton of Basel-Country, Liestal, Switzerland

<sup>o</sup> Institute of Epidemiology, Biostatistics and Prevention EBPI, University of Zurich, Switzerland

<sup>p</sup> University Hospital of Old Age Psychiatry, University of Bern, Switzerland

<sup>q</sup> University Hospital of Psychiatry Zurich, Department of Geriatric Psychiatry, Zurich, Switzerland

<sup>r</sup> Department of Geriatrics, Inselspital, Berne University Hospital, University of Berne, Switzerland

<sup>s</sup> General Practitioner, Basel, Switzerland

<sup>t</sup> Department of Internal Medicine, Rehabilitation and Geriatrics, University Hospitals and University of Geneva, Switzerland

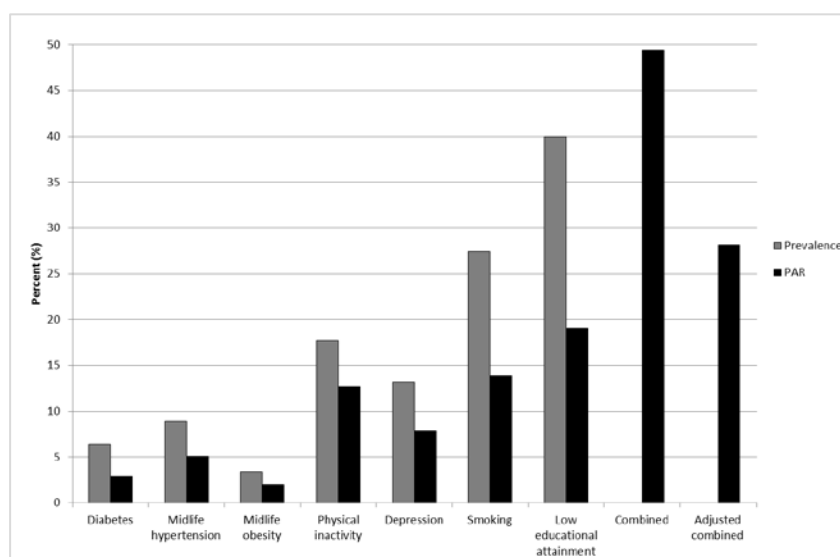
### Summary

Because of the worldwide aging of populations, Alzheimer's disease and other dementias constitute a devastating experience for patients and families as well as a major social and economic burden for both healthcare systems and society. Multiple potentially modifiable cardiovascular and lifestyle risk factors have been associated with this disease. Thus, modifying these risk factors and identifying protective factors represent important strategies to prevent and delay disease onset and to decrease the social burden. Based on the cognitive reserve hypothesis, evidence from epidemiological studies shows that low education and cognitive inactivity constitute major risk factors for dementia. This indicates that a cognitively active lifestyle may protect against cognitive decline or delay the onset of dementia. We describe a newly developed preventive programme, based on this evidence, to stimulate and increase cognitive activity in older adults at risk for cognitive decline. This programme, called "BrainCoach", includes the technique of "motivational interviewing" to foster behaviour change. If the planned feasibility study is successful, we propose to add BrainCoach as a module to the already existing "Health Coaching" programme, a Swiss preventive programme to address multiple risk factors in primary care.

**Key words:** *Alzheimer's disease; cognitive impairment; dementia; prevention; cognitive reserve; BrainCoach; protective factors; motivational interviewing*

### Introduction

The increase of life expectancy over the last century is paralleled by an elevated number of individuals with dementia, placing an enormous social and economic burden on society and healthcare systems, in addition to the devastating consequences for patients and their families. According to the World Alzheimer Report 2015, an estimated 47 million people worldwide suffer from dementia [1]. Based on current simulation models, the number of cases is expected to at least double every 20 years, reaching almost 132 million cases by 2050. However, recent reports suggest that the age-specific incidence of dementia might be decreasing in persons with at least a high school diploma, possibly owing to an improvement in cardiovascular health [2, 3]. Nevertheless, and irrespective of how fast the growth in the number of people with dementia will be, the economic impact associated with dementia is huge and increasing. Worldwide, the current total costs have increased by 35% in the last five years and were estimated to be USD 818 billion in 2015, representing 1% of the global gross domestic product [1]. These costs include direct medical care costs (dementia treatment in primary and secondary care), direct social care costs (community care professionals and residential homes) and informal care costs (unpaid care by family and others) [1].

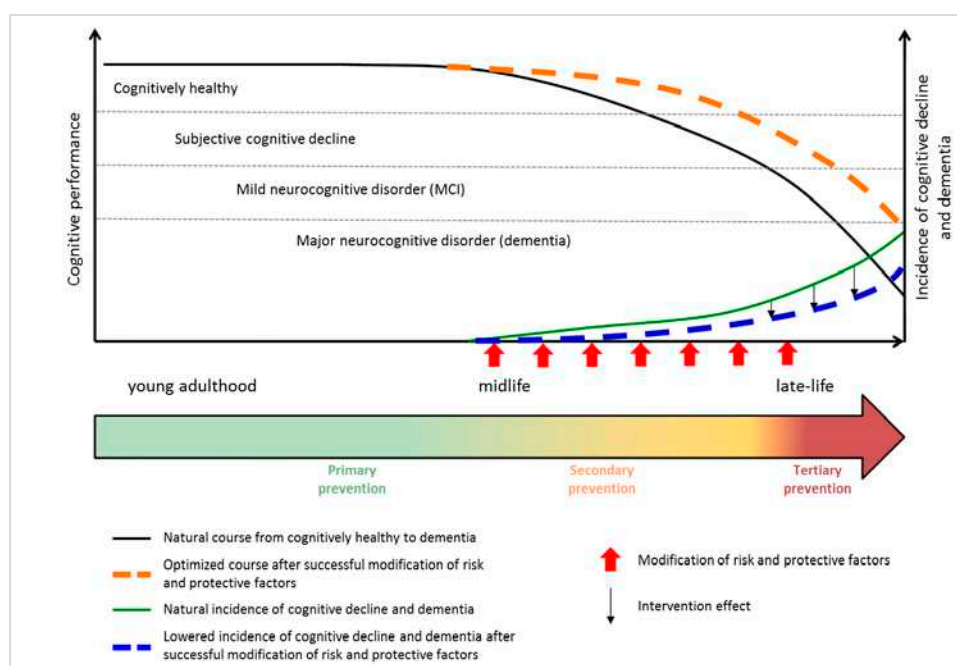


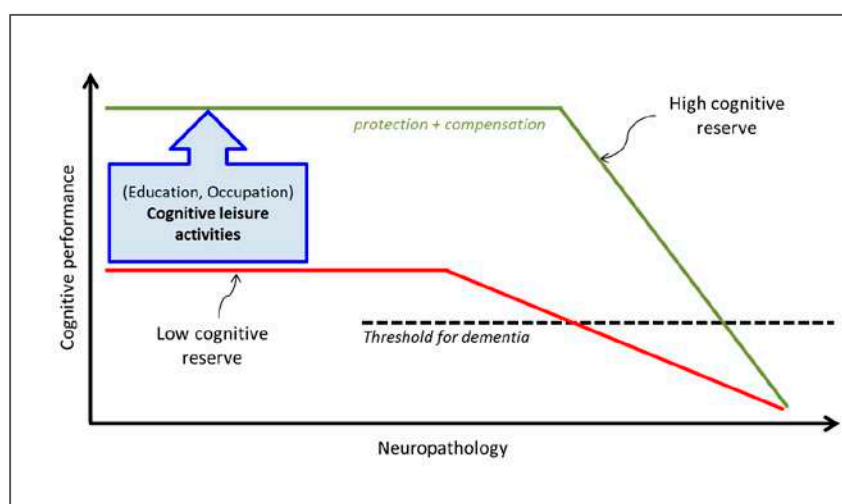
**Figure 1:** Prevalence and estimates for population-attributable risks for Alzheimer's disease in 2010. Data source: Norton et al. [11]. PAR = population-attributable risk, the proportion of Alzheimer's disease cases in the population that can be attributed to individual risk factors calculated by using the population prevalence and the relative risk of the risk factor. Combined = calculated prevalence and PAR for the seven individual risk factors combined, assuming independence of the risk factors. Adjusted combined = calculated prevalence and PAR for all seven risk factors combined with adjustment for non-independence of the risk factors.

In Switzerland, based on current simulation models, the number of people with dementia was estimated to be 119 000 in 2015, and this number is predicted to increase up to 300 000 by 2050 [4]. Annually, there are 27 000 new cases of dementia. The annual costs amount to approximately CHF 7 billion, imposing an enormous economic burden on Swiss society [5].

Although several causes of dementia exist, we will focus this review on its most common cause, Alzheimer's disease. Alzheimer's disease is clinically characterised by an insidious onset and a progressive deterioration of cognitive function, which typically starts with a decline in memory functions [6, 7]. Pathologically, Alzheimer's disease is characterised by increased levels of extracellular amyloid- $\beta$ , intracellular hyperphosphorylated tau proteins, and neuronal and synaptic loss in the neocortex [8, 9]. Despite decades of research, the pathological mechanisms underlying these disease-related changes still remain largely unclear. However, there is a broad consensus that Alzheimer's disease has a complex multifactorial aetiology and is modulated by various risk factors [10–13]. While advancing age [14]

and specific genetic predispositions (e.g., *APOE- $\epsilon 4$*  [15, 16]) are well-recognised unmodifiable main risk factors for sporadic Alzheimer's disease, additional potentially modifiable factors have been linked to the development of the disease. Specifically, observational studies indicate that cardiovascular risk factors (e.g., hypertension, diabetes, cerebrovascular disease, obesity, metabolic syndrome), lifestyle factors (e.g., unhealthy diet, smoking, high alcohol intake, low cognitive, social and physical activity, chronic stress) and psychosocial factors (e.g., lack of a rich social network, depressive symptoms) have an impact on the risk for Alzheimer's disease and other forms of dementia (for an overview see [12, 17–19]). Additionally, individual risk factors are often closely linked and thus co-occur during a person's lifetime: A recent estimate by Norton et al. [11] implies that, taking into account the interdependency of these factors, about one third of Alzheimer's disease cases worldwide may be attributable to seven potentially modifiable risk factors: diabetes, midlife hypertension, midlife obesity, depression, physical inactivity, smoking, and low educational attainment (fig. 1; see also [10]).





**Figure 3:** Illustration of the association between the emergence of dementia-associated neuropathology, its clinical expression and cognitive reserve. Figure adapted from [45]; reproduced with permission. Educational attainment and occupational challenges can usually no longer be changed in individuals aged 50 years and older. However, cognitive leisure activities may increase their cognitive reserve and thus lead to a delay in the emergence of cognitive decline.

Whereas current pharmacological and nonpharmacological treatments may decelerate disease progression, no curative or disease-modifying intervention exists to prevent the pathogenesis of dementia [20, 21]. Thus, there is a pressing need to identify preventive measures and strategies aiming to maintain brain health and delay cognitive decline. Importantly, because neurodegenerative disorders such as Alzheimer's disease have a long "silent" phase with no or only very subtle symptoms [22], such preventive programmes should optimally be implemented at the earliest possible time when cognitive impairments are not yet manifest [23–25]. Figure 2 illustrates that preventive strategies require a lifespan perspective. Thus, children and adolescents need to be targeted with regard to education and, starting at midlife, optimal management of potential risk factors is essential [26].

Different modifiable factors to preserve cognitive health have been described. A *healthy diet* (e.g., Mediterranean) rich in antioxidants, vitamins (e.g., vitamins B<sub>12</sub>, E and D) and polyunsaturated fatty acids (e.g., omega-3 [27]) may lower the risk of cognitive decline and dementia by reducing, for example, the risk for cardiovascular diseases [28, 29]. However, although findings from different studies suggest that specific dietary patterns or nutritional components may represent promising interventions in delaying cognitive decline, evidence in this regard is still weak and further investigation on this topic is needed [30, 31]. Additionally, *physical activity* is also known to exert beneficial effects on brain health. Promising results from different observational and intervention studies, as well as systematic reviews, examining the association between physical activity and the risk of cognitive impairment and dementia, yielded promising results, with moderate to strong effects of physical activity on brain health. These results indicate that individuals with a physically active lifestyle exhibit less cognitive decline [32–35], reduced brain atrophy [36] and increased hippocampal volume [37] compared with people with a sedentary lifestyle. A third important protective factor for the maintenance of brain health is *cognitive activity*. This aspect will be reviewed in more detail below and a new module within the Swiss Health Coaching programme [38], the "BrainCoach", which focuses on cognitive activity as a preventive measure of cognitive decline, is introduced.

### Cognitive activity as a modifiable protective factor for cognitive decline

As shown in figure 1, low educational attainment [11] or cognitive inactivity [10] constitutes the largest single risk factor for Alzheimer's disease. Certainly, high educational attainment will not prevent pathological brain changes; however, a number of studies indicate that higher educational attainment is related with higher levels of cognitive performance and seems to buffer negative effects and mitigate clinical symptoms in everyday life [2, 39–43]. The rationale behind this observation is the hypothesis that higher educational attainment results in an increased cognitive reserve [42, 44]. This so-called cognitive reserve hypothesis implies that individuals with higher levels of brain

activity (e.g., through individual or synergistic contributions of high educational/occupational attainment and maintained cognitive activity up until old age) may better cope with brain pathology and are able to compensate for brain damage much longer because of increased synaptic densities and a more complex and efficient structure of neural networks [23, 42]. Thus, people with the same extent of pathological brain changes may exhibit different clinical manifestations of the disease depending on their level of cognitive reserve [39] (fig. 3, [44]).

Importantly, a person with a high cognitive reserve will have a steeper decline once symptoms are manifest, as a result of higher pathological accumulations in the brain, until cognitive dysfunctions are clinically perceivable [44].

These findings are supported by several studies reporting reduced incidence rates of cognitive impairment and dementia in older adults with a high educational attainment [2, 39–43]. Additionally, an analysis from Barnes and Yaffe [10] indicates that the relative risk of developing dementia (the ratio of the probability of developing dementia in an at-risk group compared with a no-risk group) in people with a low education (primary education only) is 59% higher than in people with a higher education.

However, older adults experiencing a cognitive decline have obviously already completed their formal and occupational education. The cognitive reserve, however, is not influenced by education alone. Retrospective studies indicate that significant associations exist between cognitively activating leisure activities, engagement in social activities and the level of cognitive performance, and the risk of dementia [45–47]. Moreover, studies show that performing cognitively stimulating leisure activities later in life may somewhat compensate for a low educational attainment [48, 49]. Thus, cognitive reserve is not a static condition, but can be influenced and enhanced at any point in someone's lifetime.

The great diversity of cognitive tasks and the variability in the durations of exposure to cognitive tasks in different studies investigating the association between cognitive activity and risk of dementia meant that some studies also had inconclusive findings (see for example [50]). Nevertheless, there is substantial evidence that participating in cognitive activities conveys beneficial effects for the maintenance of brain health and may delay cognitive decline [46, 47]. Various experimental studies on rodents [50, 51] and imaging studies on humans [52–54] suggest that a mentally stimulating environment promotes neurotrophic changes in the hippocampal formation, neurogenesis and synaptic density. For example, a study by Lazarov et al. [55] with transgenic mice corroborated the idea that a cognitively stimulating environment (housing in a cave with running wheels, colourful tunnels and assorted toys) results in an increased clearance of amyloid- $\beta$  deposits compared with mice held in standard housing. Additionally, an imaging study by Valenzuela et al. [52] with healthy older human adults showed that participants with high levels of mental activity (in the domains of education, occupation, creative arts, reading, writing, socialising and day-to-day habits) across their lifespan (young adult-



hood, middle age and late life) exhibited a reduced rate of hippocampal atrophy compared with those with low levels.

A Cochrane review [56] examining the effect of cognitive training (the structured practice of tasks targeting specific domains of cognitive functioning) with 36 included studies involving healthy older participants or people with mild cognitive impairment provided evidence for an improvement in immediate and delayed verbal recall compared with participants without training. However, this positive effect did not exceed the improvements in active control groups receiving “only” nonspecific cognitive stimulation, such as reading, playing board games or dancing, which may significantly reduce the risk for cognitive decline or dementia (see also for example [47, 48, 57]). Moreover, various studies revealed that musical activities (playing an instrument or singing) enhances performance in different cognitive domains (attention, executive functions) by promoting neural plasticity and increasing grey matter volume in frontal, motor, parietal and temporal (e.g., hippocampal) areas [53, 54, 57–59].

In summary, there is hopeful evidence that nonpharmacological interventions in stages with no or very little cognitive impairment may be effective in delaying (further) cognitive decline. Optimally, such a programme should address all possible preventive aspects: dietary habits, physical activity, intake of toxic substances (smoking behaviour and alcohol consumption) and cognitive activity.

## Prevention studies with a multidimensional approach

Although observational studies confirm the association between the modifiable risk factors mentioned and Alzheimer’s disease, results from intervention studies investigating the effect of these factors in delaying the onset of cognitive decline or Alzheimer’s disease are mixed. These inconsistent findings may have resulted from various methodological problems including small samples, short intervention periods with short follow-up, inappropriate timing (too late to obtain a significant intervention effect [24]) or a mono-interventional approach investigating only one risk factor [19]. However, as the underlying pathology of Alzheimer’s disease is multifactorial, measures addressing multiple target areas aiming to modify vascular and lifestyle factors simultaneously seem more appropriate.

To date, there are three large ongoing European intervention studies targeting simultaneously multiple risk factors: the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER [60, 61], the Prevention of Dementia by Intensive Vascular Care (PreDIVA [62, 63], study and the study Multidomain Alzheimer Preventive Trial (MAPT [64–66]). Until now, only preliminary results from these studies have been published. In 2011, the European Dementia Prevention Initiative (EDPI; <http://www.edpi.org/>) was launched to combine the valuable information collected in the three ongoing European trials mentioned above. The aim of this initiative is to improve and promote the collaboration between researchers involved in the field of dementia prevention to combine experience and datasets, and better to define target populations, intervention strategies and methodological challenges in large dementia prevention trials [24]. Based on the studies mentioned above, an innovative and interactive Internet intervention platform for the treatment of cardiovascular disease in older people, called Healthy Ageing Through Internet Counselling in the Elderly (HATICE), was initiated as an additional project by the members of the EDPI (<http://www.hatice.eu/>). An additional initiative from Switzerland named “EviPrev” is based on current scientific data and focuses on evidence-based prevention and early detection of potentially chronic diseases (short interventions on physical activity, nutrition, smoking, alcohol consumption and screening for high blood pressure, dyslipidaemia, diabetes, breast cancer, colon cancer, and others) in the primary healthcare setting. Although this project is not considered to be a prevention study with a multidimensional approach, it has an important impact on cognitive health by systematically recording cardiovascular risk factors. A systematic assessment of these risk factors, which significantly affect cognitive health, is crucial for effective treatments and successful lifestyle interventions [67, 68].

## Health Coaching: a multidimensional counselling programme to promote health behaviour in the primary care setting

Based on the findings summarised so far, an additional multidimensional and structured health programme of counselling in primary care practice called “Health Coaching” was developed by the Swiss College of Primary Care Medicine (<http://www.gesundheitscoaching-khm.ch/>) [38]). Designed for general practitioners (GPs), the primary aim of this programme is to promote health behaviour in the Swiss population and prevent chronic diseases (e.g., stroke, coronary heart disease, cardiovascular disease) by targeting the most important contributors to disease burden including smoking, alcohol consumption, body weight, dietary habits, level of physical activity, and coping strategies with stress [38, 69]. The aim is to give GPs the tools to motivate their patients and support them during the implementation of a healthier lifestyle. Patients are involved in the decision process and share the responsibility for their health with the practitioner. Thus, an important aspect of Health Coaching is that patient and health professional meet on equal terms and jointly plan a step-by-step health programme based on the patient’s individual preferences and abilities [38]. The programme also emphasises the high importance of the GPs’ communication skills and offers specific training programmes in “motivational interviewing” (see below) within this programme [70]. In a nonrandomised study, the programme showed high acceptability, feasibility and improvements in health-related behaviour [38]. Although Health Coaching as a nonpharmacological programme is quite comprehensive and probably sufficient for individuals who are still in the workforce, it could benefit from an additional module focusing on cognitive activity for patients who are beyond retirement or who exhibit subtle cognitive problems.

## BrainCoach: a programme to promote cognitive activity

### Cognitive activity

Based on scientific data reviewed above we have developed a cognitive activity module to complement the Health Coaching programme. This programme, named “BrainCoach”, was specifically created for older adults at risk for cognitive impairment who might be, for example, in the so-called “silent phase” of Alzheimer’s disease [22]. It is meant to be implemented in the primary care setting and to be conducted by the GPs and other healthcare professionals (e.g., psychologists). The primary purpose of this module is – in accordance with the theory of cognitive reserve described above and the rule of “Use it or lose it!” – to support older adults and promote their motivation to maintain and increase brain health by increasing their cognitive activity. The programme addresses especially older adults feeling cognitively “bored” in everyday life, individuals shortly before retirement or individuals with subtle cognitive alterations. The promotion of the activity will be achieved by use of a specific folder (A4-format) including information about cognitive activity and its effects on brain health, communication skills (motivational interviewing) and a structured questionnaire as a guideline (working sheet) to evaluating the patients’ current cognitive activity and increase their motivation to find and implement a cognitive activity in their daily life. The BrainCoach intentionally does not include specific cognitive exercises, but highlights the importance of eliciting the patients’ motivation to find a cognitive activity that they like to perform regularly (e.g., something they performed earlier in their life). In case the patients cannot think of any cognitive activity they would like to engage in, the “BrainCoach” module offers a range of different cognitive activities – a “cognitive buffet” (different activities depicted in colour photographs) – from which the patients may choose the ones they loved to perform. Possible activities include those that can be performed individually, such as doing artwork, solving crossword puzzles, singing, playing a musical instrument, or reading books/newspapers. Activities carried out in groups have an additional stimulating component, especially due to the need of social interactions. Examples of these kinds of activities include language courses, dancing classes, singing in a choir, reading circles, attending university for seniors, playing board games, or attending cultural events with friends (e.g., theatre, cinema, and

concerts). This list included in the BrainCoach programme cannot be exhaustive, since a variety of additional activities may positively affect brain health. The patients are free to choose something from this list or to engage in another cognitively stimulating activity. The BrainCoach programme is cost-free; however, costs associated with the chosen activities have to be covered by the patients.

## Motivational interviewing

Mathematically speaking, it would make the most sense to especially inspire patients with a low cognitive reserve to (newly) engage in cognitive activities, since these individuals have the largest room for improvement (see fig. 3). Thus, the technique used to motivate patients will be critical. The main technique used in the module BrainCoach, analogous to Health Coaching, is motivational interviewing [71], a well-known client-centred and collaborative counselling technique that has frequently and successfully been applied in general healthcare settings and health promotion [72]. Briefly, eliciting people's intrinsic motivation appears to be a key factor to achieve long-lasting behavioural change [73–75]. For example, in BrainCoach a cognitive activity is chosen from the cognitive buffet because of the patient's personal interest in the activity. Its motivation is more likely to be intrinsic, because the patient probably chose this activity for being enjoyable, pleasurable, or giving satisfaction. Importantly, because patient and health practitioner work together at ground level to identify a suitable cognitive activity, engagement in this activity is not extrinsically motivated: the patient does not engage in this activity to receive a reward, or because of feeling obliged. Importantly, motivational interviewing is based on the principles of a good and equal partnership/collaboration between the GP / healthcare professional and the client, the evocation of a client's personal values and intrinsic motivation, and the client's autonomy to decide what to do (or not). Motivational interviewing can be used in a brief intervention format, making it suitable for the primary care setting. As motivating and supporting patients to make health-related behavioural changes represent a challenge for GPs, profound communication skills are crucial for successful counselling. Within BrainCoach, a training programme for GPs in motivational interviewing will be developed. The BrainCoach module, including the folder, the “cognitive buffet” and a structured questionnaire (worksheet) based on the communication skills included in motivational interviewing is currently being tested in a pilot study (feasibility, acceptance of the documents and the concept), which will be finalised and evaluated by March 2017. Its acceptance and feasibility by the patients and the impact on cognition and dementia incidence will be evaluated more extensively afterwards, in a comprehensive study with an adequate and robust study design.

## Conclusions

Because of demographic change, dementia represents a major healthcare issue for our society. Although the underlying pathogenesis of Alzheimer's disease is not fully understood, a number of observational studies provide strong evidence for an adverse effect of multiple cardiovascular and lifestyle risk factors [12]. In this regard, prevention strategies are needed to manage and lower the increase of dementia cases influenced by these risk factors. Delaying cognitive decline and dementia would have a huge impact on its incidence and prevalence. Specifically, a 10–20% reduction of the seven main risk factors for Alzheimer's disease (diabetes, midlife hypertension, midlife obesity, physical inactivity, depression, smoking, low educational attainment) would decrease Alzheimer's disease prevalence by 8–15% by 2050 [11]. Additionally, estimates from a projection model imply that interventions with the potential to delay disease onset or progression by only 1 year would reduce the number of Alzheimer's disease patients by about 11% (9 million cases [75]). Understanding the contribution and the impact of different lifestyle factors on disease development will have an important influence on future disease management and treatment since many of these risk factors are modifiable. Thus, prevention programmes and strategies targeting the modification of these factors seem a viable and reasonable approach to mitigate and delay cognitive decline and dementia [13]. Various factors including a healthy diet, smoking cessation, a physically active lifestyle and cognitive activity have been proposed to exert protective effects on

both physical and mental health. The Health Coaching programme developed by the Swiss College of Primary Care Medicine represents a comprehensive concept simultaneously targeting multiple risk factors. However, scientific evidence supports the importance of cognitive activity to maintain or increase cognitive reserve. Therefore, the module BrainCoach may represent a promising tool. Motivational interviewing as an empathetic, nonconfrontational and collaborative communication method has been shown to be effective for long-term behavioural change in several areas. The Health Coaching programme together with the BrainCoach, using the motivation interviewing counselling technique, could be a valuable, effective and low-cost approach to maintain both, physical and mental health. These programmes have important and promising implications for preventive intervention against cognitive decline and dementia.

## Correspondence:

Andreas U. Monsch  
Memory Clinic  
University Centre for Medicine of Aging Basel  
Felix Platter Hospital  
Burgfelderstrasse 101  
CH-4012 Basel  
Andreas.Monsch[at]unibas.ch

## Financial disclosure

This article and the development of the BrainCoach programme are financially supported by an unrestricted grant from Vifor Pharma.

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